



- 1. A method to identify an agent that alters adeno-associated virus transduction of a mammalian cell, comprising:
 - a) contacting the mammalian cell with the agent and virus; and
 - b) detecting or determining whether virus transduction is altered.

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- 2. The method of claim 1 wherein the cell is a mammalian lung cell.
- 10 3. The method of claim 1 wherein the cell is a mammalian liver cell.
 - 4. The method of claim 1 wherein the cell is a human cell, canine cell, murine cell, rat cell or rabbit cell.
- 15 5. The method of claim 1 wherein the transduction is enhanced.

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6. The method of claim 1 wherein endosomal processing is enhanced.

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- 7. The method of claim 1 wherein the agent is an endosomal protease inhibitor.
- 8. The method of claim 7 wherein the agent is a cysteine protease inhibitor.

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- 9. The method of claim 1 wherein the agent is a peptide or analog thereof.
- 10. The method of olaim 1 wherein the virus is recombinant adenoassociated virus.
- 11. The method of claim 10 wherein the recombinant virus encodes a therapeutic peptide or polypeptide.



12. The method of claim 10 wherein the recombinant virus comprises a marker gene or a selectable gene.



13. A method to alter adeno-associated virus transduction of a mammalian lung cell, comprising: contacting the mammalian lung cell with an amount of an agent and an amount of virus effective to alter virus transduction.

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14. A method to alter adeno-associated virus transduction of a mammalian liver cell, comprising: contacting the mammalian liver cell with an amount of an agent and an amount of virus effective to alter virus transduction.

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15. A method to alter the expression of a transgene in a mammalian lung cell, comprising: contacting the mammalian lung cell with an amount of an agent and an amount of recombinant adeno-associated virus comprising the transgene so as to alter expression of the transgene.

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16. A method to alter the expression of a transgene in a mammalian liver cell, comprising: contacting the mammalian liver cell with an amount of an agent and an amount of ecombinant adeno-associated virus comprising the transgene so as to alter expression of the transgene.

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17. A method comprising contacting a mammal subjected to gene therapy with recombinant adeno-associated virus comprising a transgene with an amount of an agent effective to alter expression of the transgene in the cells of the mammal.

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18. The method of claim 13, 14, 15, 16, or 17 wherein endosomal processing of the virus is altered.

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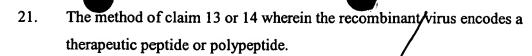
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- The method of claim 13 or 14 wherein the virus is recombinant adenoassociated virus.
- 20. The method of claim 19 wherein the recombinant virus encodes a therapeutic peptide or polypeptide.

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- 22. The method of claim 15, 16, or 17 wherein the recombinant virus encodes a therapeutic peptide or polypeptide.
- 23. The method of claim 13, 14, 15, 16 or 17/wherein the cell is contacted with the agent before the cell is contacted with the virus.
- 24. The method of claim 13, 14, 15, 16/or 17 wherein the cell is contacted with the virus before the cell is contacted with the agent.
 - 25. The method of claim 13, 14,/15, 16 or 17 wherein virus transduction is enhanced.
 - 26. The method of claim 15, 16 or 17 wherein transgene expression is enhanced.
 - 27. The method of claim 17 wherein expression is altered in lung cells.
 - 28. The method of claim 17 wherein expression is altered in liver cells.

The method of claim 1, 13, 14, 15, 16 or 17 wherein the agent is a compound of formula (I): R_1 -A/(B)_n-C wherein R_1 is an N-terminal 25 amino acid blocking group; each A and B is independently an amino acid; C is an amino acid wherein the terminal carboxy group has been replaced by a formyl (CHO) group; and n is 0, 1, 2, or 3; or a pharmaceutically acceptable salt thereof.

- The method of claim 29 wherein R_1 is (C_1-C_{10}) alkanoyl. 30 30.
 - 31. The method of claim 29 wherein R_1 is acetyl or benzyloxycarbonyl.



- 32. The method of claim 29 wherein each A and B is independently alanine, arginine, glycine, isoleucine, leucine, valine, nor-leucine or nor-valine.
- 33. The method of claim 29 wherein each A and B is isoleucine.

- 34. The method of claim 29 wherein C is alanine, arginine, glycine, isoleucine, leucine, valine, nor-leucine or nor-valine, wherein the terminal carboxy group has been replaced by a formyl (CHO) group.
- 10 35. The method of claim 29 wherein C is nor-leucine or nor-valine, wherein the terminal carboxy group has been replaced by a formyl (CHO) group.
 - 36. The method of claim 29 wherein R₁ is (C₁-C₁₀)alkanoyl or benzyloxycarbonyl; A and B are each isoleucine; C is nor-leucine or norvaline, wherein the terminal carboxy group has been replaced by a formyl (CHO) group; and N is 1.

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37. The method of claim 1, 13, 14, 15, 16 or 17 wherein the agent is a compound of formula (II):

$$\begin{array}{c|c} R_6 & O & R & R_8 \\ R_2 & N & N & N & CHO \\ \hline (II) & & & & \\ \end{array}$$

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wherein

R₂ is an N-terminal amino acid blocking group;

 R_3 , R_4 , and R_5 are each independently hydrogen, (C_1-C_{10}) alkyl,

aryl or $aryl(C_1-C_1)$ alkyl; and

 R_{6} , R_{7} , and R_{8} are each independently hydrogen, $(C_{1}-C_{10})$ alkyl,

25 aryl or $aryl(C_{1}-C_{10})$ alkyl; or a pharmaceutically acceptable salt thereof.

38. The method of claim 37 wherein R_2 is (C_1-C_{10}) alkanoyl.

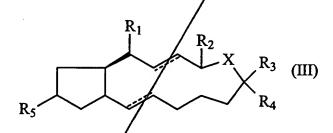


- 39. The method of claim 37 wherein R_2 is acetyl or benzyloxycarbonyl.
- 40. The method of claim 37 wherein R_3 is hydrogen or (C_1-C_{10}) alkyl.
- 5 41. The method of claim 37 wherein R_3 is 2-methylpropyl.
 - 42. The method of claim 37 wherein R_4 is hydrogen or (C_1-C_{10}) alkyl.
 - 43. The method of claim 37 wherein R_4 is 2-methylpropyl.

- 44. The method of claim 37 wherein R_5 is hydrogen or (C_1-C_{10}) alkyl.
- 45. The method of claim 37 wherein R₅ is butyl or propyl.
- 15 46. The method of claim 37 wherein R_2 is acetyl or benzyloxycarbonyl; R_3 and R_4 are each 2-methylpropyl; R_5 is butyl or propyl; and R_6 , R_7 , and R_8 are each independently hydrogen.
 - 47. The method of claim 1, 13, 14, 15, 16 or 17 wherein the agent is a compound of formula (III):



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wherein

 R_1 is H, halogen, (C_1-C_{10}) alkyl, (C_1-C_{10}) alkenyl, (C_1-C_{10}) alkynyl, (C_1-C_{10}) alkoxy, (C_1-C_{10}) alkanoyl, (=O), (=S), OH, SR, CN, NO₂, trifluoromethyl or (C_1-C_{10}) alkoxy, wherein any alkyl, alkenyl, alkynyl, alkoxy or alkanoyl may optionally be substituted with one or more halogen, OH, SH, CN, NO₂, trifluoromethyl, NRR or SR, wherein each R is independently H or (C_1-C_{10}) alkyl;

$$R_2$$
 is (=0) or (=S)

 R_3 is H, (C_1-C_{10}) alkyl, (C_1-C_{10}) alkenyl, (C_1-C_{10}) alkynyl, (C_1-C_{10}) alkoxy or (C_3-C_8) cycloalkyl, wherein any alkyl, alkenyl, alkynyl, alkoxy or cycloalkyl may optionally be substituted with one or more halogen, OH, CN, NO₂, trifluoromethyl, SR, or NRR, wherein each R is independently H or (C_1-C_{10}) alkyl;

 R_4 is H, (C_1-C_{10}) alkyl, (C_1-C_{10}) alkenyl, (C_1-C_{10}) alkynyl, (C_1-C_{10}) alkoxy or (C_3-C_8) cycloalkyl, wherein any alkyl, alkenyl, alkynyl, alkoxy or cycloalkyl may optionally be substituted with one or more halogen, OH, CN, NO_2 , trifluoromethyl, SR, or NRR, wherein each R is independently H or (C_1-C_1)

10 C_{10})alkyl;

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R₅ is H, halogen, (C_1-C_{10}) alkyl, (C_1-C_{10}) alkenyl, (C_1-C_{10}) alkynyl, (C_1-C_{10}) alkoxy, (C_1-C_{10}) alkanoyl, (=O) (=S), OH, SR, CN, NO₂ or trifluoromethyl, wherein any alkyl, alkenyl, alkoxy or alkanoyl may optionally be substituted with one or more halogen, OH, SH, CN, NO₂, trifluoromethyl, NRR or SR, wherein each R is independently H or (C_1-C_{10}) alkyl; and

X is O, S or NR wherein R is H or (C_1-C_{10}) alkyl, or a pharmaceutically acceptable salt thereof.

- 48. The method of claim 47 wherein R₁ is halogen, CN, NO₂, trifluoromethyl or OH.
 - 49. The method of claim 47 wherein R_1 is OH.
 - 50. The method of claim 47 wherein R_2 is (=0).
 - 51. The method of claim 47 wherein R_3 is H or (C_1-C_{10}) alkyl.
 - 52. The method of claim 47 wherein R_3 is methyl.
- 30 53. The method of claim 47 wherein R_4 is H or (C_1-C_{10}) alkyl.
 - 54. The method of claim 47 wherein R_4 is H.

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- 55. The method of claim 47 wherein R₅ is halogen, CN, NO₂, trifluoromethyl or OH.
- 56. The method of claim 47 wherein R_5 is OH.

- 57. The method of claim 47 wherein X is O or S.
- 58. The method of claim 47 wherein X is O.
- 10 59. The method of claim 47 wherein both ---- are a single bond.
 - 60. The method of claim 47 wherein one ---- is a double bond.
 - 61. The method of claim 47 wherein both ---- are a double bond.

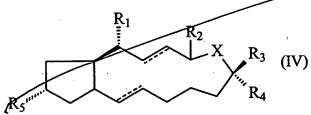
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62. The method of claim 45 wherein R₁ is OH, R₂ is (=O), R₃ is methyl, R₄ is H, R₅ is OH, X is O, and both ----- are a double bond.

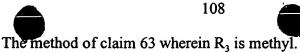
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63. The method of claim 44 wherein the compound is a compound of formula (IV):



- 64. The method of claim 63 wherein R₁ is halogen, CN, NO₂, trifluoromethyl or OH.
- 25 65. The method of claim 63 wherein R_1 is OH.
 - 66. The method of claim 63 wherein R_2 is (=0).
 - 67. The method of claim 63 wherein R_3 is H or (C_1-C_{10}) alkyl.



- 69. The method of claim 63 wherein R_4 is H or (C_1-C_{10}) alkyl.
- 5 70. The method of claim 63 wherein R_4 is H.
 - 71. The method of claim 63 wherein R₅ is halogen, CN, NO₂, trifluoromethyl or OH.
- 10 72. The method of claim 63 wherein R_5 is OH.
 - 73. The method of claim 63 wherein X is O or S.
 - 74. The method of claim 63 wherein X is O.

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- 75. The method of claim 63 wherein both ---- are a single bond.
- 76. The method of claim 63 wherein one ---- is a double bond.
- 20 *77*. The method of claim 63 wherein both ---- are a double bond.
 - 78. The method of claim 63 wherein R_1 is OH, R_2 is (=0), R_3 is methyl, R_4 is H, R_5 is OH, X is O, and both ---- are a double bond.

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Nor)17 wherein the agent inhibits 79. The method of claim 1, 13, the activation of ubiquitin, the transfer of ubiquitin to the ubiquitin carrier protein, ubiquitin Mgase, or a combination thereof.

or\17 wherein the agent inhibits 80. The method of claim/1, 13, 14 ubiquitin ligase.

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81. The method of claim 1, 13, 14, 15, 15, or 17 wherein the agent is a compound/of formula (IV):



$$R \longrightarrow A \longrightarrow A_1 \longrightarrow R_1$$

wherein R is hydrogen, an amino acid, or a peptide, wherein the N-terminus amino acid can optionally be protected at the amino group with acetyl, acyl, trifluoroacetyl, or benzyloxycarbonyl; A is an amino acid or a direct bond; A_1 is an amino acid; and R_1 is hydroxy or an amino acid, wherein the C-terminus amino acid can optionally be protected at the carboxy group with (C_1-C_6) alkyl, phenyl, benzyl ester or amide (e.g., $C(=O)NR_2$, wherein each R is independently hydrogen or (C_1-C_6) alkyl);

- or a pharmaceutically acceptable salt thereof.
 - 82. The method of claim 81 wherein the agent is H-Leu-Ala-OH, H-His-Ala-OH, or a combination thereof.



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The method of claim 1/13, 14, 15, 15 or 17 further comprising administering a second agent that enhances the activity of the agent.

84. The method of claim 83 wherein the second agent is EGTA.

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